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CORRESPONDENCE

Paternal somatogonadal COL2A1 mosaicism causing recurrence of severe type 2 collagenopathy

To the Editor:

We read with interest the report by Yamamoto et al. (2020) describing a mild type 2 collagenopathy recurring due to maternal somatogonadal mosaicism. We describe a similar phenomenon but in a severe type 2 collagenopathy with paternal somatogonadal mosaicism.

Case History: A 39-year-old primigravida pregnant as a result of IVF treatment (due to maternal severe endometriosis) was found to have a fetus with a skeletal dysplasia at 22 weeks gestation. Scan confirmed limbs measuring 15 weeks. Invasive prenatal investigations were declined but noninvasive testing was negative for achondroplasia and thanatophoric dysplasia using PCR analysis of cell free fetal DNA from maternal plasma for the FGFR3 gene. A live born infant was delivered by elective caesarian section at 38^{+6} weeks and intubated for 24 hr and a diagnosis of hypochondrogenesis was made on radiological and genetic assessment. Unfortunately, pediatric pathology was not available so no postmortem was possible after final extubation at 24 hr. Examination confirmed a small thoracic cage and short limbs (Figure 1) and limited supine radiological examination confirmed lack of pelvic bone ossification, 11 paired ribs with flaring of the anterior ends, extremely short long bones with metaphyseal flaring and pointing, and no evidence of polydactyly (Figure 2). WHO child growth standard measurements (de Onis, 2015) included length 36 cm (z score = −8.973), weight 2,926 g (z score = −1.590), and head circumference 35.5 cm (z score = −0.351). A clinical radiographic diagnosis of hypochondrogenesis was made. Exome Sequencing analysis of a virtual panel of skeletal genes confirmed the baby was heterozygous for the NM_001844.4(COL2A1_v001): c.1403G > A variant resulting in the protein change NM_001844.4 (COL2A1_i001):p.(Gly468Asp), consistent with a severe type 2 collagenopathy. The variant was confirmed using Sanger sequencing.

A further pregnancy ensued with a second IVF embryo successfully implanted. Scan at 20 weeks gestation suggested similar findings to the first pregnancy with short limbs of around 16 weeks. Prenatal diagnosis by amniocentesis confirmed the fetus carried the same mutation as the first child and which was also detected in their asymptomatic father. The pregnancy was terminated with no post mortem.

Further detailed clinical assessment of the father at age 45 revealed normal stature (his height 173 cm, his eldest sister 165 cm, his younger sister 165 cm, his father 177 cm, maternal height not available) appropriate for his family and normal radiological imaging on skeletal survey with normal eye assessment and no evidence of any collagenopathy. Sanger sequencing analysis of his blood DNA confirmed 22% mosaicism; buccal cells confirmed ~25% mosaicism and cultured skin fibroblasts ~20% mosaicism (Figure 3). The testing confirmed paternal somatogonadal mosaicism and the couple decided on donor insemination of any further stored eggs given the high risk of further recurrence of ~50%.

This finding confirms that type 2 collagenopathies may arise from somatogonadal mosaicism. Like the case by Yamamoto (Yamamoto

FIGURE 1 Intubated neonate showing short limbs and small thorax and distended abdomen, with facial dysmorphism including flat face and microretrognathia [Color figure can be viewed at wileyonlinelibrary.com]

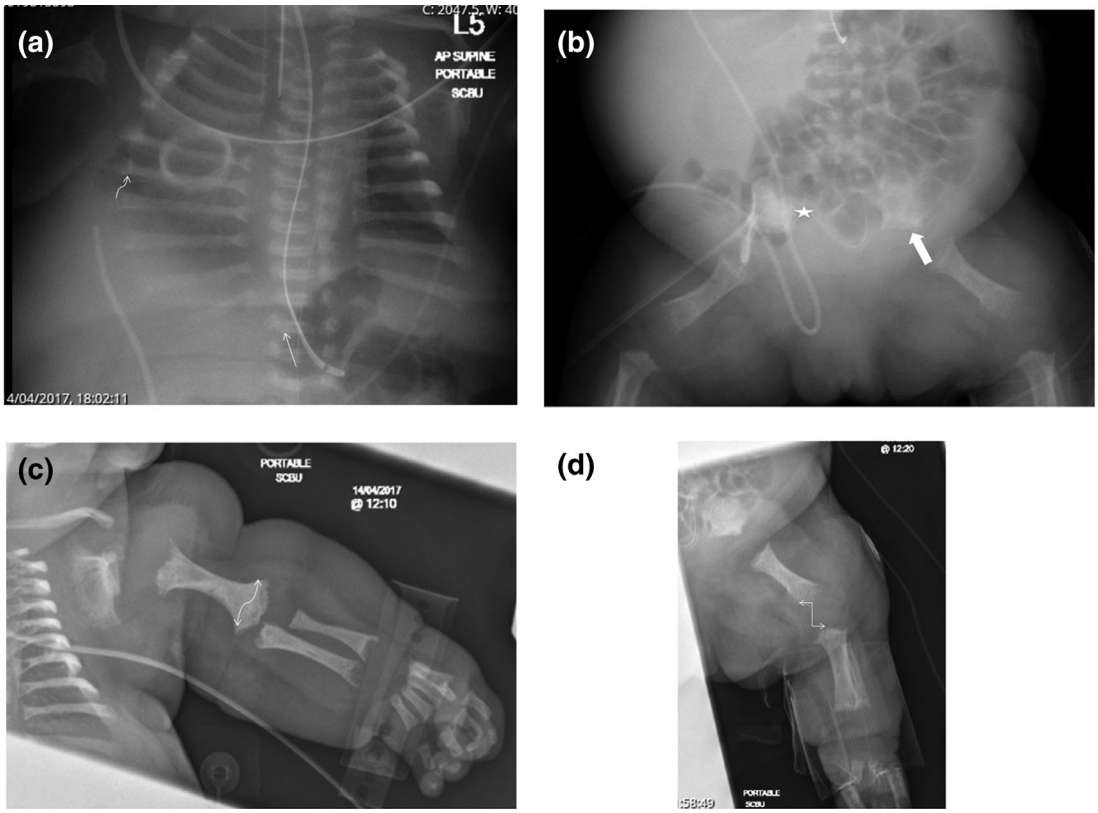

FIGURE 2 Radiology showing changes suggestive of hypochondrogenesis in (a) anteroposterior (AP) chest showing platyspondyly (arrow), small thorax, metaphyseal cupping of the anterior ribs (curved arrow), (b) AP pelvis showing absent ischiatic bones (broad arrow) and underdeveloped lower pelvis (star), (c) AP left humerus showing metaphyseal broadening and cupping (curved double arrow), and (d) AP left femur showing short broad tubular bones (double arrow)

et al., 2020) where there was a nonlethal dysplasia with normal maternal clinical assessment, we show that severe lethal type 2 collagenopathy mutations may be carried without apparent clinical effects by a clinically normal parent. Okamoto et al. (2012) described a case of Torrance lethal dysplasia due to a NM_001844.4 (COL2A1_v001):c.3545G > A (p.Gly1182Asp) variant (transcript information inferred) in exon 50 of the encoded triple helical region of COL2A1, in two siblings with similar clinical findings to our case. At the time the parents did not consent to sampling, but it remains likely that somatogonadal mosaicism in one parent was the cause in that report. Although there is no clear evidence that collagenopathies have a higher risk of parental mosaicism compared to other disorders, it may be that the severe phenotypic effects in nonmosaic cases make consideration of testing for parental mosaicism more likely in phenotypically unaffected parents. There may be a threshold effect where high mosaicism levels may trigger symptoms or signs but a low level does not and different tissues may vary in that threshold.

This case illustrates that parental testing should be strongly considered after the clinical presentation of mild or severe type 2 collagenopathy as even in lethal cases one parent may have no apparent clinical findings so testing may give important clinical information on the recurrence risks and allow future reproductive options to be considered for the parents.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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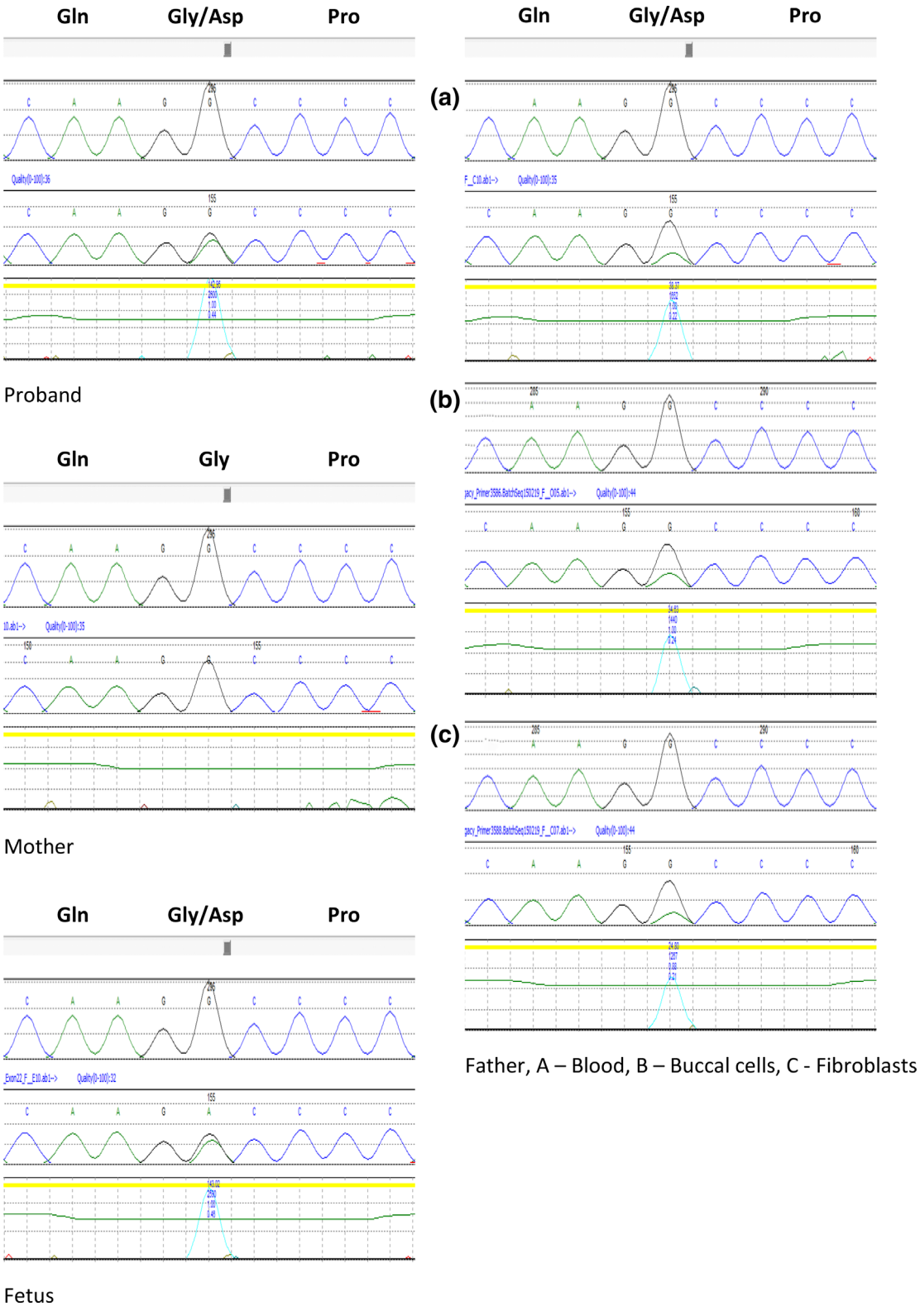

FIGURE 3 Sequencing data from the proband, mother and fetus (top), and in sampled tissues from the father A—blood, B—buccal cells, C—fibroblasts (bottom) [Color figure can be viewed at wileyonlinelibrary.com]

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